FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
0273-0009	
U.S. APPLICATION NO (IF KNOWN, SEE 37 CFR	
To Be Determined 10/069357	
INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE
PCT/EP00/07993 ✓	16-August-2000 ✓
PRIORITY DATE CLAIMED	
25-August-2000 ✓	

TITLE OF INVENTION
PHOSPHOLIPID GEL

APPLICANT(S) FOR DO/EO/US
IBSCHER, Bernd; and FRIDRICH, Ruland

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include itens (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☒ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☐ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

1) International Patent Application as Published Under PCT, Publication No. WO01/13887; 2) Written Opinion; 3) Reply to Written Opinion; 4) postcard.

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
To Be Determined 10/069357	PCT/EP00/07993	0273-0009

24. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS PTO USE ONLY
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	**$1040.00**	
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	**$890.00**	
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	**$740.00**	
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	**$710.00**	
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	**$100.00**	
ENTER APPROPRIATE BASIC FEE AMOUNT =		**$890.00**
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).		**$0.00**

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	31 - 20 =	11	x $18.00	**$198.00**
Independent claims	1 - 3 =	0	x $84.00	**$0.00**
Multiple Dependent Claims **(check if applicable)**.			☒	**$280.00**
TOTAL OF ABOVE CALCULATIONS			=	**$1,368.00**
☐ Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.				**$0.00**
SUBTOTAL			=	**$1,368.00**
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).			+	**$0.00**
TOTAL NATIONAL FEE			=	**$1,368.00**
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐				**$0.00**
TOTAL FEES ENCLOSED			=	**$1,368.00**
				Amount to be: refunded $
				charged $

a. ☒ A check in the amount of **$1,368.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **50-0622** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

SHANKS & HERBERT
TransPotomac Plaza
1033 North Fairfax Street, Suite 306
Alexandria, Virginia 22314
(703) 683-3600
(703) 683-9875 (facsimile)

SIGNATURE

Joseph G. Contrera
NAME

44,628
REGISTRATION NUMBER

25-February-2002
DATE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: IBSCHER et al.	
	Art Unit: To Be Assigned
Serial No.: To Be Assigned	Examiner: To Be Assigned
Filed: Herewith	Atty. Docket: 0273-0009
For: Phospholipid Gel.	

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination of the above-identified application, Applicants herewith respectfully requests the following amendments:

IN THE CLAIMS:

Delete claims 1 - 23.

Insert the following new claims 24 - 55. A copy of the new claims is enclosed herewith as Appendix A.

24. (new) A phospholipid gel comprising: a) a range of about 5-60% by weight of at least one phospholipid; b)at least 1% by weight of at least one dihydric or trihydric C_2-C_4 -alcohol; c)a range of about 0.5-35% by weight of at least one polyhydric alcohol selected from the group consisting of tetrahydric alcohols, pentahydric alcohols, hexahydric alcohols and sugars; and d)water to 100% by weight, the percent by weight data in each case relating to the total gel.

25. (new) The phospholipid gel of claim 24 further comprising one or more additives having cosmetic actions selected from the group consisting of vitamins, sunscreen filters and alpha-hydroxy acids.

26.(new) The phospholipid gel of claim 24, wherein the sugar is selected from the group consisting of mono-, di-, and oligosaccharides.

27. (new) The phospholipid gel of claim 24, wherein the polyhydric alcohol is a sugar alcohol selected from the group consisting of glucose, fructose, sucrose, trehalose, xylitol, maltitol, inositol, sorbitol and mannitol.

28. (new) The phospholipid gel of claim 24 comprising 2-20% by weight of at least one polyhydric alcohol selected from the group consisting of tetrahydric alcohols, pentahydric alcohols, hexahydric alcohols and sugars.

29. (new) The phospholipid gel of claim 24 comprising 2.5-10% by weight of at least one polyhydric alcohol selected from the group consisting of tetrahydric alcohols, pentahydric alcohols, hexahydric alcohols and sugars.

30. (new) The phospholipid gel of claim 24 comprising about 1-40% by weight of at least one dihydric or trihydric C_{2-4} -alcohol.

31. (new) The phospholipid gel of claim 24 comprising about 15-40% by weight of at least one di- or trihydric C_{2-4}-alcohol.

32. (new) The phospholipid gel of claim 24, wherein the dihydric or trihydric C_{2-4}- alcohol is at least one alcohol selected from the group consisting of propanediol, propylene glycol and glycerol.

33. (new) The phospholipid gel of claim 32 comprising about 15-30% by weight of propylene glycol and about 0-10% by weight of glycerol.

34. (new) The phospholipid gel of claim 33 comprising about 2.5 - 7.5% by weight of glycerol.

35. (new) The phospholipid gel of claim 24 or 25 further comprising up to 10% by weight of at least one alcohol selected from the group consisting of ethanol, 1-propanol and 2-propanol.

36. (new) The phospholipid gel of claim 24, wherein said phospholipid comprises a phosphatidylcholine content of at least 70% by weight based on the phospholipid.

37. (new) The phospholipid gel of claim 24, wherein said phospholipid is further comprised of a nonhydrogenated phospholipid having a phosphatidylcholine content of at least 70% by weight based on the phospholipid.

38. (new) The phospholipid gel of claim 24, wherein said phospholipid comprises a mixture of phosphatidylcholine and lysophosphatidylcholine, said mixture containing at least 75% by weight of phosphatidylcholine.

39. (new) The phospholipid gel of claim 24, wherein said phospholipid comprises a hydrogenated phospholipid having at least 90% by weight of phosphatidylcholine.

40. (new) The phospholipid gel of claim 24, comprising about 5-25% by weight of at least one phospholipid.

41. (new) The phospholipid gel of claim 24, comprising about 15-25% by weight of at least one phospholipid.

42. (new) The phospholipid gel of claim 24 or 35, further comprising a pharmaceutically active compound selected from the group consisting of: anti-inflammatories, nonsteroidal antirheumatics, corticoids, peptides, hormones, enzymes, nucleic acids, virustatics, vitamins, local anesthetics, antimycotics, antibiotics, circulation-promoting agents, α-sympatho-mimetics, antipsoriatics and nose drops.

43. (new) The phospholipid gel of claim 42, wherein said pharmaceutically active compound is selected from the group consisting of: acyclovir, heparin, diclophenac, hydrocortisone, xylometazoline, diphenhydramine,
calcitonin, cyclosporin, indomethacin and insulin.

44. (new) The phospholipid gel of any one of claims 24, 25,35 or 42, further comprising at least one buffer having a high buffer capacity in the range of about pH 5.5-8.0.

45. (new) The phospholipid gel of claim 44 comprising at least one buffer having a high buffer capacity of about pH 6.5.

46. (new) The phospholipid gel of claim 44, wherein said buffer is selected from the group consisting of: BISTRIS, phosphate buffer, hydrogencarbonate buffer, maleate buffer, HEPES, TRIS and MOPS.

47. (new) A cosmetically acceptable formulation comprising the phospholipid gel as claimed in any one of claims 24, 25, 35 or 44.

48. (new) A pharmaceutically acceptable formulation comprising the phospholipid gel as claimed in any one of claims 24, 35, 42 or 44.

49. (new) The cosmetically acceptable formulation of claim 47 for use in dermatological applications.

50. (new) The pharmaceutically acceptable formulation of claim 48 for use in dermatological applications.

51. (new) The cosmetic formulation of claim 47 for use as a lip gel, nasal gel, ophthalmic gel, vaginal gel or anal gel.

52. (new) The pharmaceutical formulation of claim 48 for use as a lip gel, nasal gel, ophthalmic gel, vaginal gel or anal gel.

53.(new) A process for the production of a phospholipid gel as claimed in any one of claims 24, 25, 35, 42,or 44, wherein said gel is prepared by mixing the constituents under vacuum or under an inert gas atmosphere.

54. (new) A process for the production of the cosmetically acceptable formulation of claim 47 wherein said formulation is prepared by mixing its constituents under vacuum or under an inert gas atmosphere.

55. (new) A process for the production of the pharmaceutically acceptable formulation of claim 48 wherein said formulation is prepared by mixing its constituents under vacuum or under an inert gas atmosphere.

IN THE SPECIFICATION:

Insert the following Section Headings:

Insert **"FIELD OF THE INVENTION"** as line 19 on page 1.

Insert **"BACKGROUND OF THE INVENTION"** after line 22 on page 1.

Insert **"SUMMARY OF THE INVENTION"** after line 22 on page 3.

Insert **"BRIEF DESCRIPTION OF THE DRAWINGS"** after line 11 on page 15.

Insert **"DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS"** after line 11 on page 16.

Delete Paragraph 1, Page 6, lines 1 - 14. A marked-up version of said paragraph is enclosed herewith as Appendix B.

Replace the deleted paragraph with the following clean version:

Clean Version of Replacement Paragraph 1, Page 6, lines 1 - 11.

range. A content of 1-40% by weight is preferred, particularly preferably 15-30% by weight. If propylene glycol is employed on its own as the alcohol component, the propylene glycol content in the gel should preferably be between 25 and 30% by weight. If glycerol is employed on its own as the alcohol component, the glycerol content in the gel should be between 20 and 30% by weight. However, mixtures of, for example, 15-30% by weight of propylene

glycol and 0-10% by weight, in particular 2.5-7.5% by weight, of glycerol can also be present in the gel according to the invention.

REMARKS

It is respectfully requested that the Examiner enter these amendments prior to examining the application on its merits.

Respectfully submitted,

SHANKS & HERBERT

By: _____

Joseph G. Contrera
Reg. No. 44,628

Date: 2/25/02

TransPotomac Plaza
1033 N. Fairfax Street
Suite 306
Alexandria, VA 22314
(703) 683-3600

APPENDIX A: Patent Claims

24. (new) A phospholipid gel comprising: a) a range of about 5-60% by weight of at least one phospholipid; b) at least 1% by weight of at least one dihydric or trihydric C_2-C_4 -alcohol; c) a range of about 0.5-35% by weight of at least one polyhydric alcohol selected from the group consisting of tetrahydric alcohols, pentahydric alcohols, hexahydric alcohols and sugars; and d) water to 100% by weight, the percent by weight data in each case relating to the total gel.

25. (new) The phospholipid gel of claim 24 further comprising one or more additives having cosmetic actions selected from the group consisting of vitamins, sunscreen filters and alpha-hydroxy acids.

26. (new) The phospholipid gel of claim 24, wherein the sugar is selected from the group consisting of mono-, di-, and oligosaccharides.

27. (new) The phospholipid gel of claim 24, wherein the polyhydric alcohol is a sugar alcohol selected from the group consisting of glucose, fructose, sucrose, trehalose, xylitol, maltitol, inositol, sorbitol and mannitol.

28. (new) The phospholipid gel of claim 24 comprising 2-20% by weight of at least one polyhydric alcohol selected from the group consisting of tetrahydric alcohols, pentahydric alcohols, hexahydric alcohols and sugars.

29. (new) The phospholipid gel of claim 24 comprising 2.5-10% by weight of at least one polyhydric alcohol selected from the group consisting of tetrahydric alcohols, pentahydric alcohols, hexahydric alcohols and sugars.

30. (new) The phospholipid gel of claim 24 comprising about 1-40% by weight of at least one dihydric or trihydric C_{2-4} -alcohol.

31. (new) The phospholipid gel of claim 24 comprising about 15-40% by weight of at least one di- or trihydric C_{2-4}-alcohol.

32. (new) The phospholipid gel of claim 24, wherein the dihydric or trihydric C_{2-4}- alcohol is at least one alcohol selected from the group consisting of propanediol, propylene glycol and glycerol.

33. (new) The phospholipid gel of claim 32 comprising about 15-30% by weight of propylene glycol and about 0-10% by weight of glycerol.

34. (new) The phospholipid gel of claim 33 comprising about 2.5 - 7.5% by weight of glycerol.

35. (new) The phospholipid gel of claim 24 or 25 further comprising up to 10% by weight of at least one alcohol selected from the group consisting of ethanol, 1-propanol and 2-propanol.

36. (new) The phospholipid gel of claim 24, wherein said phospholipid comprises a phosphatidylcholine content of at least 70% by weight based on the phospholipid.

37. (new) The phospholipid gel of claim 24, wherein said phospholipid is further comprised of a nonhydrogenated phospholipid having a phosphatidylcholine content of at least 70% by weight based on the phospholipid.

38. (new) The phospholipid gel of claim 24, wherein said phospholipid comprises a mixture of phosphatidylcholine and

lysophosphatidylcholine, said mixture containing at least 75% by weight of phosphatidylcholine.

39. (new) The phospholipid gel of claim 24, wherein said phospholipid comprises a hydrogenated phospholipid having at least 90% by weight of phosphatidylcholine.

40. (new) The phospholipid gel of claim 24, comprising about 5-25% by weight of at least one phospholipid.

41. (new) The phospholipid gel of claim 24, comprising about 15-25% by weight of at least one phospholipid.

42. (new) The phospholipid gel of claim 24 or 35, further comprising a pharmaceutically active compound selected from the group consisting of: anti-inflammatories, nonsteroidal antirheumatics, corticoids, peptides, hormones, enzymes, nucleic acids, virustatics, vitamins, local anesthetics, antimycotics, antibiotics, circulation-promoting agents, α-sympatho-mimetics, antipsoriatics and nose drops.

43. (new) The phospholipid gel of claim 42, wherein said pharmaceutically active compound is selected from the group consisting of: acyclovir, heparin, diclophenac, hydrocortisone, xylometazoline, diphenhydramine, calcitonin, cyclosporin, indomethacin and insulin.

44. (new) The phospholipid gel of any one of claims 24, 25,35 or 42, further comprising at least one buffer having a high buffer capacity in the range of about pH 5.5-8.0.

45. (new) The phospholipid gel of claim 44 comprising at least one buffer having a high buffer capacity of about pH 6.5.

46. (new) The phospholipid gel of claim 44, wherein said buffer is selected from the group consisting of: BISTRIS,

phosphate buffer, hydrogencarbonate buffer, maleate buffer, HEPES, TRIS and MOPS.

47. (new) A cosmetically acceptable formulation comprising the phospholipid gel as claimed in any one of claims 24, 25, 35 or 44.

48. (new) A pharmaceutically acceptable formulation comprising the phospholipid gel as claimed in any one of claims 24, 35, 42 or 44.

49. (new) The cosmetically acceptable formulation of claim 47 for use in dermatological applications.

50. (new) The pharmaceutically acceptable formulation of claim 48 for use in dermatological applications.

51. (new) The cosmetic formulation of claim 47 for use as a lip gel, nasal gel, ophthalmic gel, vaginal gel or anal gel.

52. (new) The pharmaceutical formulation of claim 48 for use as a lip gel, nasal gel, ophthalmic gel, vaginal gel or anal gel.

53.(new) A process for the production of a phospholipid gel as claimed in any one of claims 24, 25, 35, 42,or 44, wherein said gel is prepared by mixing the constituents under vacuum or under an inert gas atmosphere.

54. (new) A process for the production of the cosmetically acceptable formulation of claim 47 wherein said formulation is prepared by mixing its constituents under vacuum or under an inert gas atmosphere.

55. (new) A process for the production of the pharmaceutically acceptable formulation of claim 48 wherein said formulation is

prepared by mixing its constituents under vacuum or under an inert gas atmosphere.

APPENDIX B: MARKED-UP VERSION OF REPLACEMENT PARAGRAPH

range. A content of 1-40% by weight is preferred, particularly preferably 15-30% by weight, [where, however, lower concentrations are also possible, in particular if an additional preservative is incorporated.] If propylene glycol is employed on its own as the alcohol component, the propylene glycol content in the gel should preferably be between 25 and 30% by weight. If glycerol is employed on its own as the alcohol component, the glycerol content in the gel should be between 20 and 30% by weight. However, mixtures of, for example, 15-30% by weight of propylene glycol and 0-10% by weight, in particular 2.5-7.5% by weight, of glycerol can also be present in the gel according to the invention.

August 16 2000
K/T/sm

Merckle GmbH
Ludwig-Merckle-Str. 3

D-89143 Blaubeuren

Phospholipid gel

The present invention relates to a phospholipid gel, and to cosmetic and pharmaceutical formulations which contain these gels.

Phospholipid gels are known in the prior art. These gels have found interest as pharmaceutical vehicles. The phospholipid is not only a vehicle for the active substance here, but also controls the bioavailability of the pharmaceutical. The reason for this is the special molecular arrangement of the phospholipids, which can form stable liposomes consisting of bilayers. The active compound is better absorbed, since the phospholipids make possible an easier absorption of the active compound into the target cells.

A process for the preparation of liposome solutions which can contain a pharmacological active compound is disclosed, for example, in EP-B-0 069 307. In the

preparation of these solutions, liposome gels are firstly obtained which can be used, for example, as an ointment base. In order to suppress gelling of the liposome solutions obtained, EP-B-0 069 307 proposes adding an electrolyte such as, for example, a physiological buffer system or a sugar.

A liposomal composition for medicinal or cosmetic purposes which comprises 0.5-10% of phospholipids, 20-50% of a C_{2-4}-alcohol, 0-30% of glycol, at least 20% of water and at least one active compound is disclosed in WO 95/35095.

DE 195 20 659 discloses a pharmaceutical preparation which, in addition to the active compound acyclovir, contains 5-35% by weight of a phospholipid, 15-50% by weight of an alcohol and 79-0% by weight of water, the alcohol being a di- and/or trihydric C_{2-5}-alcohol on its own or as a mixture with ethanol, 1-propanol and/or 2-propanol.

US patent no. 5,820,848 discloses liposome-containing gels which can contain a short-chain alcohol such as methanol, ethanol, propanol, isopropanol or n-butanol or polyols such as glycerol and ethylene glycol.

The phospholipid gels known in the prior art have the disadvantage that they easily liquefy on application to the skin. Liquefaction of the gel strand is all the more strongly pronounced the higher the perspiration content on the skin. This is particularly disadvantageous in the case of gels which are intended for application to the mucous membranes. Patients frequently feel the liquefaction and consequently the watery feeling on application of the conventional phospholipid gels to be unpleasant.

Moreover, known phospholipid gels have the disadvantage that they can liquefy even on incorporation of a

pharmaceutical, buffer or salt, in particular if readily soluble substances, such as, for example, diphenhydramine HCl, are incorporated. In these cases, the preparations may flow even under their own weight.

This effect is known, for example, from DE 40 03 783 A1. In this, a phospholipid-containing gel is disclosed which is preserved using alcohols such as ethanol or 2-propanol. According to examples 7 and 9-12, the gels obtained liquefy on addition of a buffer or salt solution.

An object of the present invention thus consists in making available a phospholipid gel which, compared with known phospholipid gels, has a higher stability on application to the skin and in the presence of an incorporated pharmaceutical, buffer or salt.

According to the invention, it has now been found that this problem can be solved by incorporating into the phospholipid gel a tetra-, penta- or hexahydric alcohol, and/or sugar.

The present invention thus relates to a phospholipid gel, comprising

5-60% by weight of at least one phospholipid;
at least 1% by weight of at least one di- or trihydric C_{2-4}-alcohol;
0.5-35% by weight of at least one tetra-, penta- or hexahydric alcohol and/or at least one sugar;
optionally one or more additives and water to 100% by weight,

the % by weight data in each case relating to the entire gel.

The phospholipid preparation according to the invention contains phospholipids which are preferably of natural

origin. In particular, phospholipids from plants, such as, for example, soybean lecithin, are suitable. The phospholipids can be characterized by means of the phosphatidylcholine content, which is the main ingredient of phospholipids.

In principle, according to the invention either hydrogenated and/or nonhydrogenated phospholipids can be employed. In the case of the nonhydrogenated phospholipids, the phosphatidylcholine content is at least approximately 70% by weight based on the phospholipid, preferably the phosphatidylcholine content is at least approximately 75% by weight. In the case of the hydrogenated phospholipids, the phosphatidylcholine content is a least approximately 90% by weight.

The phospholipid used according to the invention can also be a mixture of various phospholipids and in particular a mixture of phosphatidylcholine and lysophosphatidylcholine. In such a mixture, the weight ratio of phosphatidylcholine to lysophosphatidylcholine should be between 97:3 and 40:60, higher phosphatidylcholine contents of at least 75% by weight (in the case of nonhydrogenated phospholipids) and preferably at least 90% by weight (in the case of hydrogenated phospholipids) based on the total phospholipid being preferred.

Known phospholipids which fulfill these properties are obtainable, for example, from Nattermann Phospholipid GmbH under the names Phospholipon® 80 and Phospholipon® 90 H. Phospholipon® 80 comprises approximately 76% of phosphatidylcholine and approximately 3% of lysophosphatidylcholine, Phospholipon® 90 H, a hydrogenated phosphatidylcholine, comprises at least 90% of phosphatidylcholine and at most 4% of lysophosphatidylcholine. Phospholipon® 80 is also obtainable as a 75% strength solution in ethanol (NAT

8539) and as a 60% strength solution in propylene glycol (NAT 8450). Phospholipids from other manufacturers, however, can also be used for the gel according to the invention.

In one embodiment, hydrogenated phospholipids are employed. An advantage of this embodiment is that smaller amounts of phospholipids can be added. Thus, for example, approximately 20% of nonhydrogenated phospholipids can be replaced by approximately 10% of hydrogenated phospholipids so that a cost-saving results.

The content of phospholipids in the gel should be between 5 and 60% by weight. Below 5%, no gel formation is possible, and above 60%, acceptable gel can no longer be formulated. Preferably, the phospholipid content in the gel according to the invention is 5-35% by weight and particularly preferably 15-25% by weight.

As a further constituent, the gel according to the invention comprises at least 1% by weight, preferably 20 to 30% by weight, of at least one di- or trihydric C_{2-4}-alcohol. In higher concentrations, this alcohol acts as a preservative. Moreover, this alcohol acts as a solvent for the phospholipid and can also serve as a solubilizer for the active compound. Furthermore, this constituent can serve as a penetration enhancer. Finally, the moistness of the skin can also be increased. A suitable dihydric alcohol is in particular a propanediol, propylene glycol (1,2-propanediol) having proven particularly advantageous. A trihydric alcohol which can be employed is, for example, glycerol. The gel can also contain mixtures of various types of these alcohols.

The content of the di- or trihydric C_{2-4}-alcohol in the gel according to the invention can vary over a wide

range. A content of 1-40% by weight is preferred, particularly preferably 15-30% by weight, where, however, lower concentrations are also possible, in particular if an additional preservative is incorporated. If propylene glycol is employed on its own as the alcohol component, the propylene glycol content in the gel should preferably be between 25 and 30% by weight. If glycerol is employed on its own as the alcohol component, the glycerol content in the gel should be between 20 and 30% by weight. However, mixtures of, for example, 15-30% by weight of propylene glycol and 0-10% by weight, in particular 2.5-7.5% by weight, of glycerol can also be present in the gel according to the invention.

As an essential constituent which decreases the proneness to liquefaction of the phospholipid gel, the gel according to the invention contains 0.5-35% by weight of at least one tetra-, penta- or hexahydric alcohol or sugar. The term "sugar" is understood according to the invention as meaning mono-, di- and/or oligosaccharides. The tetra-, penta- or hexahydric alcohols are preferably sugar alcohols. These include, for example, glucose, fructose, sucrose, trehalose, xylitol, maltitol, inositol, sorbitol and mannitol. Mixtures of the additives mentioned, namely mixtures of various alcohols and/or various sugars, such as, for example, a mixture of sorbitol and glucose, can also be used.

In order to decrease the proneness of the phospholipid gel to liquefaction, the content of the polyhydric alcohol or sugar in the preparation can be varied over a wide range. The amount to be employed depends, for example, on the presence of other preservatives, the liquefying action of a pharmaceutical which may be present and the nature of a buffer which may be employed and on further additives present. Furthermore, the content of higher-hydric alcohol or

sugar should be tailored to the intended use of the gel according to the invention. If the gel according to the invention is intended, for example, for application to the nasal mucous membranes, it should be taken into account that in the nose, on the one hand, increased moistness is present and on the other hand salts are present which, as electrolytes, favor liquefaction of the gel. If the gel according to the invention, however, is to be applied, for example, only to dry skin, the liquefying action is smaller on account of a lower moisture and salt content on the skin. The alcohol, sugar or sugar alcohol content in the gel can be tailored according to these requirements. In the case of gels which can come into contact with the gastrointestinal tract, such as, for example, gels for lips and/or oral mucous membranes, it is to be taken into account that certain sugars produce a sweet taste. On the other hand, however, it may be preferred not to use sugars if the gel is also to be suitable for diabetics. Sugar alcohols are then preferred.

A polyhydric alcohol or sugar content in the range from 2-20% by weight and in particular 2.5-10% by weight has proven advantageous.

If the gel according to the invention is to be employed as a pharmaceutical formulation, it additionally comprises one or more pharmaceutical active compounds. The gel according to the invention is particularly advantageous for active compounds which are readily water-soluble substances, since these regularly already lead to liquefaction of conventional gels on incorporation. Advantageously, the gel according to the invention, however, is also suitable for poorly or nonsoluble pharmaceutical active compounds, since it then displays its liquefaction-inhibiting action on application, for example to the skin or mucous membrane.

The pharmaceutical active compound can be selected, for example, from the group consisting of anti-inflammatories, nonsteroidal antirheumatics, corticoids, peptides, hormones, enzymes, nucleic acids, virustatics, vitamins, local anesthetics, antimycotics, antibiotics, antipsoriatics, circulation-promoting agents, α-sympathomimetics and nose drops. Preferably, virustatics, in particular acyclovir, corticoids, hormones and in particular peptides, can be incorporated into the gel according to the invention.

Pharmaceutical active compounds which may be mentioned are, for example, acyclovir, heparin, diclofenac, hydrocortisone, xylometazoline, cyclosporin, diphenhydramine, calcitonin and indomethacin or their pharmaceutically acceptable salt. It is an advantage of the composition according to the invention that not only the active compounds, but also pharmaceutically acceptable salts can be incorporated without problems.

The phospholipid gel preparation according to the invention also makes possible a topical application of those medicaments which cannot be administered orally and otherwise have to be administered parenterally. These active compounds are, for example, insulin, which can be absorbed, for example, via the nasal mucous membrane.

However, it is also possible, with the aid of the phospholipid gels according to the invention, to administer vaccines, hormones or nucleic acids (preferably for inoculation). On account of the phospholipids, the gels according to the invention make possible a good penetration of the skin. The phospholipid gel according to the invention therefore makes possible a noninvasive administration form of those pharmaceuticals which cannot be administered orally, such as, for example, peptides or nucleic acids (for example for inoculation). The gel structure which

can be achieved by means of the phospholipid gels according to the invention makes it possible, for example, to apply the gel preparation to the nasal mucous membranes in such a way that the active compound can readily penetrate the mucous membrane.

Instead of or in addition to pharmaceutical active compounds, the gel according to the invention, however, can also include constituents having a cosmetic action. Examples of these are vitamins, sunscreen filters or α-hydroxy acids.

As a further constituent, the gel according to the invention can contain up to 10% by weight of at least one alcohol selected from ethanol, 1-propanol and 2-propanol. These monohydric alcohols, however, are incorporated into the gel only in addition to the abovementioned di- and trihydric alcohols.

A significant advantage of the gel according to the invention consists in the fact that, on account of the stabilization of the phospholipid gel by the polyhydric alcohol, and/or sugar, present, a buffer system can be incorporated into the preparation without liquefaction of the gel occurring. The buffer should be chosen here such that it has a high buffer capacity in the range of the stability optimum of the phosphatidylcholine. The stability optimum of phosphatidylcholine is at pH 6.5, so that the buffer should have a high buffer capacity in the range from pH 5.5-8.0 and preferably approximately pH 6.5. As a result of the buffering of the gel in the range of the stability optimum of the phosphatidylcholine, the storage stability of the gel can be increased. This is to be attributed to a slowing of the hydrolysis of the phosphatidylcholine to lysophosphatidylcholine. For example, in a nonbuffered gel the decrease in the phosphatidylcholine content after 25 weeks at 41°C was 58%. In a gel which was

BISTRIS-buffered and otherwise of the same recipe, the decrease after 36 weeks at 41°C, however, was only 44%.

Buffers which have proven particularly suitable are BISTRIS (2-(bis(2-hydroxyethylimino)-2-hydroxymethyl)-1,3-propanediol) (pK_a 6.5), phosphate buffer (buffer range sec-phosphate about 6.2-8.2), hydrogencarbonate buffer (buffer range about 5.4-6.9), maleate buffer (buffer range about 6.0-6.8), TRIS: (trishydroxymethyl-aminomethane), MOPS: (3-[N-morpholino]propanesulfonic acid) and HEPES (N-[2-hydroxyethyl]piperazine-N'[2-ethanesulfonic acid). On account of its pK_a of 6.5, BISTRIS has proven particularly advantageous.

The amount of the buffer added is not particularly critical, but should be chosen to be so high that an adequate buffer action is achieved. For example, a BISTRIS concentration of approximately 0.075M (1.57% by weight) in the gel is particularly suitable.

If desired, a prespecified pH of the gel can, however, also be set by addition of an acid or alkali, such as, for example, NaOH.

The gel according to the invention can also contain further additives, such as, for example, preservatives, colorants, deodorants and taste enhancers. The taste enhancers can in particular play a role if the substances per se are otherwise not pleasant-tasting. The phospholipids obtained from soybeans are in some cases also not felt to be pleasant as regards taste.

Unlike other gel preparations, the semisolid phospholipid gel preparation according to the invention preferably contains no further thickeners, emulsifiers, consistency-imparting agents or other gel-forming agents in the conventional sense. In particular, the gel preferably contains no further gel-forming agents,

such as acrylates, cellulose derivatives, starch and starch derivatives, gelatin and alginates.

In addition to the constituents mentioned, the gel according to the invention contains water to 100% by weight. For pharmaceutical preparations, purified water according to pharmacopeia should be used.

The gel according to the invention is particularly suitable for the production of cosmetic or pharmaceutical formulations. The amount of the cosmetic substance or pharmaceutical to be incorporated into the phospholipid gel for this purpose can be varied over a wide range and depends on the substance. The person skilled in the art can easily determine suitable concentrations, for example as a function of the efficacy of the active compound and of the intended purpose of use of the gel obtained. Acyclovir can be incorporated into the preparation, for example, in an amount of approximately 5% by weight, diphenhydramine HCl in an amount of approximately 1% by weight, hydrocortisone in an amount of approximately 0.25-1% by weight, heparin Na in an amount of 60 000 I.U. and calcitonin in an amount of 100 000 I.U. Further possible active compounds and amounts of active compound can be taken from the examples.

A preferred base recipe according to the invention for pharmaceutical formulations comprises approximately 23.5% by weight of phospholipid, approximately 22.5% by weight of propylene glycol, approximately 5% by weight of ethanol, approximately 2.5% by weight of sorbitol, a BISTRIS concentration of approximately 1.57% by weight, an active compound in suitable amount and water to 100% by weight.

The cosmetic and pharmaceutical formulations according to the invention are suitable for application to the skin or mucous membrane, such as, for example, the skin

of the lip or the oral mucous membranes. Preferably, the phospholipid gel-containing formulations according to the invention, however, can also be applied to the nasal mucous membranes. Here, the effect according to the invention of the suppression of the liquefaction of the gel is particularly advantageous, since in the nose, on the one hand, increased moistness is present and on the other hand salts are also present which, as electrolytes, can lead to an increased liquefaction with conventional gels.

The phospholipid gels according to the invention can also be applied, however, even in the case of other mucous membranes. An appropriate cosmetic or pharmaceutical formulation can be, for example, a lip gel, nasal gel, ophthalmic gel, vaginal gel or anal gel, such as a hemorrhoid gel or a gel for the treatment of anal fissures.

The phospholipid gels according to the invention primarily serve for use in humans. However, it is also possible to employ these phospholipid gels in animals, such as, for example, for veterinary medical purposes, in particular for the treatment of dogs, cats or horses.

The gel according to the invention and the cosmetic or pharmaceutical formulation according to the invention can be prepared by mixing the constituents under vacuum or under an inert gas atmosphere. The mixing of the constituents and the gel formation can be carried out according to conventional processes known in the prior art. The absence of oxygen, which can be achieved by working under vacuum or an inert gas atmosphere, is advantageous here.

The gel according to the invention is preferably a gel having a semisolid consistency. The consistency of the gel can be determined using a rotary viscometer. For

the present invention and in particular also in the following examples, a rotary viscometer (RheoStress RS 150) from HAAKE was used. The measurements were carried out at 20.0°C using measuring plates having a diameter of 35 mm. The measuring gap was 0.5 mm. The measurements were carried out as oscillation measurements with shear stress requirement at constant frequency (1.0 Hz). For this, the sample was introduced into the measuring gap and the measuring body was set into an oscillating motion (oscillation requirement) and the response function of the sample was measured. An accurate description of this method is found in the HAAKE publication "Characterization of Contact Adhesives (PSA systems)" by D. Eidman.

In this measuring process, the storage modulus G′ can be determined as a component of the strain energy which can be stored elastically by the system, the loss modulus G″ as a component of the strain energy which is irreversibly converted into viscous flow by the system, and the loss angle δ as the phase delay between the oscillation requirement and response function as a function of the shear stress τ.

The flow limit of a substance or of a composition is not precisely defined. One possibility for the determination of the flow limit consists, however, in the oscillation measurement described above. With small amplitudes (shear stress τ below the flow limit), the loss angle δ of the substance does not depend on τ (viscoelastic range). Under the influence of higher shear stress, δ increases greatly, which allows a rather viscous behavior to be concluded. The critical shear stress value on the transition from the linear viscoelastic to the viscous range can be interpreted as the flow limit (cf. H.-M. Petri in the HAAKE publication "Determination of the Flow Limit in Foodstuffs"). This value can be read off from a graph in which the loss angle δ is plotted against the shear

stress τ, at the transition of the resulting curve from its virtually horizontal part to the steeper part.

An increased flow limit, that is an increased value for the critical shear stress, confirms an increased stability of the measurement sample with respect to liquefaction. Qualitatively, such an increased stability can also be recognized from an increase in the maximum storage modulus G' in a plot of G' against τ.

As guidance for the assessment of the liquefaction, a division can be used according to which a cosmetic milk has a flow limit at a critical shear stress of < 10 Pa, a lotion a flow limit at a critical shear stress of 10-20 Pa and a cream a flow limit at a critical shear stress of usually > 100 Pa. The flow limit of the gels according to the invention is preferably at a critical shear stress of above 20 Pa and particularly preferably between 20 and 200 Pa. Gels having a flow limit at a critical shear stress of below about 20 Pa begin according to experience to flow under their own weight. Semisolid gels are mainly understood in particular as meaning those gels which do not flow under their own weight.

However, it must be stressed that the above-described critical shear stress at the flow limit of the gels according to invention is of minor importance as an absolute value for the present invention, since this essentially depends on the determination method. Moreover, according to the invention it is rather significant that the sugar- or alcohol-containing gel has a higher stability to liquefaction compared with conventional, that is sugar- or alcohol-free, gels. This effect is marked by a relative increase in the critical shear stress at the flow limit or a relative increase in the maximum storage modulus G' in comparison with conventional gels.

The phospholipid gels according to the invention are distinguished in particular by the stability of their consistency to the incorporation of additives, such as pharmaceuticals or buffers, and in their application to the skin or mucous membrane. The consistency of the gels is stabilized in such a way that even on incorporation of additives the semisolid state is retained. Moreover, the properties of spreadability on application to the skin or mucous membrane are also retained.

Fig. 1 A shows the dependence of the loss angle δ as a function of the shear stress τ for a gel not according to the invention with addition of NaCl. Sometimes no NaCl (♦), sometimes 0.2% NaCl (•), sometimes 0.4% NaCl (■) and sometimes 0.8% NaCl (▲) were employed. From figure 1 A, it is evident that the shear stress τ changes with increasing salt concentration.

Fig. 1 B shows the dependence of the storage modulus G' as a function of the shear stress τ for a gel not according to the invention with addition of NaCl. Here, no NaCl (◇),0.2% NaCl (O),0.4% NaCl (□) and 0.8% NaCl (Δ) were employed in the experiment. From figure 1 B, it is evident that the maximum storage modulus G' decreases with increasing salt concentration.

Fig. 2 A shows the dependence of the loss angle δ as a function of the shear stress τ for a gel according to invention, to which various amounts of NaCl have been added. The symbols correspond to those of figure 1 A.

Fig. 2 B shows that in the gel according to the invention the values hardly change even on addition of NaCl. The meaning of the symbols of figure 2 B corresponds to that of figure 1 B. The fact that the values hardly change due to addition of NaCl shows the superiority of the gel according to invention.

Fig. 3 shows the dependence of the loss angle δ (closed symbols) and the storage modulus G' (open symbols) as a function of the shear stress τ for a gel not according to the invention with and without BISTRIS buffer.

Fig. 4 shows the dependence of the loss angle δ (closed symbols) and the storage modulus G' (open symbols) as a function of the shear stress τ for a gel according to the invention with and without BISTRIS buffer.

The invention is illustrated in more detail by the following examples without being restricted to these.

Example 1

In this example, various pharmaceutical-containing gels according to the invention are prepared. Examples 1.1 to 1.4 show that various pharmaceuticals having different solubility properties and in different concentrations can be incorporated into the preparation according to the invention.

Gels having the following compositions were prepared (details in % by weight, if not stated otherwise):

Example 1.1

Acyclovir	5.0%
Nonhydrogenated lecithin	23.5%
Propylene glycol	20.0%
Ethanol	10.0%
Sorbitol	2.5%
Phosphate buffer	0.05M
Water	to 100.0%

Example 1.2

Diphenhydramine HCl	1.0%
Nonhydrogenated lecithi	20.0%
Propylene glycol	22.5%
Ethanol	5.0%
Mannitol	5.0%
Water	to 100.0%

Example 1.3

Hydrocortisone	0.25%
Nonhydrogenated lecithin	25.0%
Propylene glycol	27.5%
Trehalose	10.0%
BISTRIS	0.075M
Water	to 100.0%

Example 1.4

Calcitonin	100,000 I. U.
Nonhydrogenated lecithin	18.0g
Propylene glycol	25.0g
Glycerol	5.0g
Sucrose	6.0g
Water	to 100.0g

Acyclovir is a substance which is poorly soluble in water. Diphenhydramine HCl is a hydrophilic substance which is very readily soluble in water as a salt. Hydrocortisone is a lipophilic substance which is more soluble in lipophilic solvents than in water. Calcitonin is a hydrophilic protein which is soluble in water.

This example shows that, with addition of pharmaceuticals having very different dissolving properties, phospholipid gels according to the invention can be obtained.

Example 2

Table 1 below contains a listing of the compositions of further gels according to the invention. In addition to a favorite base recipe, these gels contain various pharmaceuticals in various concentrations. The quantitative data of the individual constituents are stated in % by weight based on the overall composition.

Table 1

Pharmaceutical	**PL**	**PG**	**EtOH**	**BISTRIS**	**Sorbitol**
Heparin Na 60 000 I.U	23.5	22.5	5	1.57	2.5
Diclofenac Na 1%	23.5	22.5	5	1.57	2.5
Hydrocortisone 1%	23.5	22.5	5	1.57	2.5
Xylometazoline HCl 0.1%	23.5	22.5	5	1.57	2.5
Indomethacin 1%	23.5	22.5	5	1.57	2.5

PL = phospholipid (Phospholipon 80); PG = propylene glycol; EtOH = ethanol

Example 3

When incorporating pharmaceuticals or additives into phospholipid gels, electrolytes are frequently introduced into the preparations. Moreover, when applying the gels to the skin, in particular the mucous membrane, electrolytes such as, for example, salts from the perspiration are dissolved in the gels. These electrolytes can lead to a liquefaction of the gels.

This example shows the action of an addition of salt on a phospholipid gel with and without sorbitol. The base

recipe of the phospholipid gel had the following composition: 23.5% by weight of phospholipid PL80, 22.5% by weight of propylene glycol, 5% by weight of ethanol, 1.57% by weight of BISTRIS, remainder water.

0; 0.2; 0.4 and 0.8% by weight of NaCl were added to this base recipe and using the oscillation measurement generally described above, the loss angle δ and the storage modulus G' was determined for each recipe (not according to the invention) as a function of the shear stress τ. The result of these measurements is shown in figure 1 A and 1 B. It is seen that the critical shear stress, that is the shear stress value at which the curves shown climb steeply from their virtually horizontal course, falls with increasing salt concentrations. Moreover, the maximum storage modulus G' falls with increasing salt content. This shows that the flow limit of the gels falls with increasing salt content and the gels thus liquefy more easily with increasing salt concentration.

Figures 2 A and 2 B show the result of the same measurement, 2.5% by weight of sorbitol and 0.2; 0.4 and 0.8% by weight of NaCl in each case being added to the base recipe. It is seen that as a result of the addition of sorbitol the influence of the electrolyte on the flow limit and the maximum storage modulus G' of the gel is virtually suppressed.

This experiment shows that the consistency of phospholipid gels according to the invention is retained despite addition of electrolytes such as NaCl.

Analogous measurements were carried out with addition of various pharmaceuticals, such as acyclovir, heparin Na and diclofenac Na, and various sugar alcohols and sugars, such as glucose, sucrose, trehalose, xylitol and fructose, comparable results being obtained.

Example 4

In this example, a buffer was added to a base recipe of 23.5% by weight of phospholipid, 22.5% by weight of propylene glycol, 5.0% by weight of ethanol and water to 100.0% by weight without and in the presence of 2.5% of sorbitol and the effect of this addition on the proneness of the composition to liquefaction was investigated.

BISTRIS was added to the recipe as a buffer. The buffer concentration was 1.57% by weight.

The result for the oscillation measurement as described above for the sorbitol-free gels (not according to the invention) with and without BISTRIS is shown in figure 3. It is seen that the level of the storage modulus G' is lowered in the presence of BISTRIS, just as the critical shear stress, which is a measure of the flow limit.

The result of the oscillation measurement using the sorbitol-containing gels according to the invention with and without BISTRIS is shown in figure 4. It is seen that no lowering of the level of the storage modulus G' or of the critical shear stress takes place. The measured courses of the curves are virtually identical.

This example shows that the addition of sorbitol to a phospholipid gel virtually abolishes the proneness of the gel to liquefaction on addition of a buffer. By means of this, it is possible by incorporation of a buffer into a phospholipid gel to increase significantly the stability of this gel and thus the storability of this gel.

Example 5

In this example, the subjective feeling on the topical application of phospholipid gels according to the invention and not according to the invention is investigated. The compositions of the gels investigated are shown in table 2, the compositions A, B, D and F being compositions according to the invention and the sorbitol-free composition C serving as a comparison composition not according to the invention. As an additional comparison composition, a conventional acyclovir cream (composition E) was included in the test.

Table 2

	A	B	C	D	F
NAT 8450	20.0	20.0	20.0	5.0	-
PL 90 H	7.5	-	-	7.5	6.0
Propylene glycol	20.0	30.0	20.0	30.0	20.0
Glycerol	-	7.5	12.5	-	-
Sorbitol	5.0	10.0	-	10.0	10.0
Acyclovir	5.0	5.0	5.0	5.0	5.0

PL 90 H = Phospholipon® 90 H (hydrogenated)
NAT 8540 = 60% solution of Phospholipon 80 in propylene glycol

The quantitative data in table 2 are in % by weight based on the total composition, these in each case being made up to 100% by weight with water.

The study was carried out as follows. Before the start of the experiment, both lower arms and, before each application, the index finger of each patient, were wiped with Kleenex®. After each application cycle (all six bases are applied), the application sites were wiped with Kleenex®. A total of three cycles were

carried out. Per cycle, the subject once wore a strip of 1 cm length on the inside of the lower arm and spread this with the index finger. Per lower arm, three formulations were applied.

The diameter of the base spread along the arm should be at most 5 cm. The individual application sites should not intersect.

After each application cycle, the subjects were ordered to assess the spreadability on application (consistency, cosmetic feel, etc), the appearance of the formulation (hypo-/lipophilicity) and the remaining feeling after the application (stickiness, skin tautness, etc) and to assign the formulations to a rank according to their popularity. Rank 1 had the best assessment, rank 6 the worst.

The test was carried out with 13 subjects (spreadability and hydro-/lipophilicity) or 11 subjects (remaining feeling).

The evaluation was carried out according to the rank total test (L. Sachs, Statistical Methods, Planning and Evaluation, p. 85 ff). For this, the ranks which had been assigned to a composition by each subject for each investigated criterion (target criterion) were summed (rank total) and compared with one another. A lower rank total shows a greater popularity of a composition in comparison and conversely.

The results of this investigation are shown in table 3. For each composition A-F, for each target criterion (I = spreadability, II = hydro-/lipophilicity, III = remaining feeling), the rank to which each subject (1-13) has assigned this is indicated. The subject 1 has, for example, favored composition C (rank 1) in the assessment of the spreadability (target criterion I) and assessed the composition E to be the worst (rank

6). Moreover, the standard deviation (sdv), the rank total (T = total of all ranks) and the number of respective subjects (j) are indicated in the table for each composition and each target criterion.

Table 3

Sub-ject	A			B			C			D			E			F		
	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III
1	3	4	4	2	3	2	1	1	1	4	2	3	6	6	6	5	5	5
2	3	6		4	4		6	3		2	2		5	5		1	1	
3	4	6	4	3	5	1	1	4	3	2	2	5	6	3	2	5	1	6
4	3	4	4	2	2	2	5	5	5	4	3	3	6	6	6	1	1	1
5	4	6	6	3	4	3	2	2	4	6	5	5	5	3	2	1	1	1
6	1.5	2.5	2	1.5	2.5	3	4	5	1	6	4	6	5	6	5	3	1	4
7	1	1	5	2	2	6	6	6	4	3	5	1	5	3	3	4	4	2
8	2	2	2	5	3	6	4	6	4	3	5	5	6	4	1	1	1	3
9	3	1	5	4	2	3	5	5	2	1	3	4	6	4	6	2	6	1
10	2	2		4	3		5	4		3	5		6	6		1	1	
11	4	3	6	2	2	5	3	6	3	1	1	2	5	4	1	6	5	4
12	6	2	4	1	6	1	2	5	5	3	4	6	4	3	3	5	1	2

13	4	6	5	5	5	4	3	4	3	2	3	6	6	2	2	1	1	1
sdv	1.33	1.96	1.35	1.33	1.34	1.79	1.76	1.55	1.4	1.61	1.39	1.72	0.66	1.42	2.01	1.96	1.96	1.79
T	40.5	45.5	47	38.5	43.5	36	47	56	35	40	44	46	71	55	37	36	29	30
j	13	13	11	13	13	11	13	13	11	13	13	11	13	13	11	13	13	11

For a better general view, the results from table 3 are given once more in table 4 and sorted according to the target criteria (T = rank total, j = number of subjects).

5 Table 4

	I. Spreadability						II.Hydro-/lipophilicity						III. Remaining feeling					
	A	B	C	D	E	F	A	B	C	D	E	F	A	B	C	D	E	F
T	40.5	38.5	47	40	71	36	45.5	43.5	56	44	55	29	47	36	35	46	37	30
j	13	13	13	13	13	13	13	13	13	13	13	13	11	11	11	11	11	11

It is seen that the subjective feeling was preferred both for the spreadability on application and for the appearance of the formulation for the gels according to the invention (A, B, D and F) both compared with the sorbitol-free gel not according to the invention (C), and compared with the conventional cream (E). Although for the remaining feeling a composition according to the invention (F) was also favored, overall, however, no uniform picture resulted.

Merckle GmbH

Patent claims

1. A phospholipid gel, comprising

5-60% by weight of at least one phospholipid;
at least 1% by weight of at least one di- or trihydric C_{2-4}-alcohol;
0.5-35% by weight of at least one tetra-, penta- or hexahydric alcohol and/or at least one sugar;
optionally one or more additives and water to 100% by weight,

the % by weight data in each case relating to the total gel.

2. A phospholipid gel as claimed in claim 1, characterized in that the sugar is a mono-, di- and/or an oligosaccharide.

3. The phospholipid gel as claimed in claim 1 or 2, in which the phospholipid has a phosphatidylcholine content of at least 70% by weight based on the phospholipid.

4. A phospholipid gel as claimed in claim 3, in which the phospholipid is a nonhydrogenated phospholipid having a phosphatidylcholine content of at least 70% by weight based on the phospholipid.

5. A phospholipid gel as claimed in claim 4, in which the phospholipid comprises a mixture of phosphatidylcholine and lysophosphatidylcholine and this mixture contains at least 75% by weight of phosphatidylcholine.

6. A phospholipid gel as claimed in claim 1 or 2, in which the phospholipid comprises a hydrogenated phospholipid which contains at least 90% by weight of phosphatidylcholine.

7. A phospholipid gel as claimed in one of the preceding claims, comprising 5-35% by weight, preferably 15-25% by weight, of at least one phospholipid.

8. A phospholipid gel as claimed in one of the preceding claims, in which the di- or trihydric C_{2-4}-alcohol is propanediol, in particular propylene glycol, glycerol or a mixture of these alcohols.

9. A phospholipid gel as claimed in one of the preceding claims, comprising 1-40% by weight, preferably 15-40% by weight, of at least one di- or trihydric C_{2-4}-alcohol.

10. A phospholipid gel as claimed in claim 9, comprising 15-30% by weight of propylene glycol and 0-10% by weight, in particular 2.5-7.5% by weight, of glycerol.

11. A phospholipid gel as claimed in one of the preceding claims, in which the tetra-, penta- or hexahydric alcohol or sugar is selected from glucose, fructose, sucrose, trehalose, xylitol, maltitol, inositol, inositol, sorbitol and mannitol.

12. A phospholipid gel as claimed in one of the preceding claims, comprising 2-20% by weight, in particular 2.5-10% by weight, of at least one tetra-, penta- or hexahydric alcohol or sugar.

13. A phospholipid gel as claimed in one of the preceding claims, comprising a pharmaceutical active compound selected from the group consisting of anti-

inflammatories, nonsteroidal antirheumatics, corticoids, peptides, hormones, enzymes, nucleic acids, virustatics, vitamins, local anesthetics, antimycotics, antibiotics, circulation-promoting agents, α-sympathomimetics, antipsoriatics and nose drops.

14. A phospholipid gel as claimed in one of the preceding claims, comprising a pharmaceutical active compound selected from acyclovir, heparin, diclophenac, hydrocortisone, xylometazoline, diphenhydramine, calcitonin, cyclosporin, indomethacin and insulin.

15. A phospholipid gel as claimed in one of the preceding claims, comprising up to 10% by weight of at least one alcohol selected from ethanol, 1-propanol and 2-propanol.

16. A phospholipid gel as claimed in one of the preceding claims, comprising at least one buffer having a high buffer capacity in the range from pH 5.5-8.0, preferably approximately pH 6.5.

17. A phospholipid gel as claimed in claim 16, in which the buffer is selected from BISTRIS, phosphate buffer, hydrogencarbonate buffer, maleate buffer, HEPES, TRIS and MOPS.

18. A phospholipid gel as claimed in one of the preceding claims, which is free of other thickeners, emulsifiers, consistency-imparting agents and/or gel-forming agents.

19. A cosmetic or pharmaceutical formulation, comprising a phospholipid gel as claimed in one of claims 1-18.

20. A cosmetic or pharmaceutical formulation as claimed in claim 19 for topical application.

21. A cosmetic or pharmaceutical formulation as claimed in claim 19, it being a lip gel, nasal gel, ophthalmic gel, vaginal gel or anal gel.

22. The use of a phospholipid gel as claimed in one of claims 1-18 for the production of a cosmetic or pharmaceutical formulation.

23. A process for the production of a phospholipid gel as claimed in one of claims 1-18 or of a cosmetic or pharmaceutical formulation as claimed in one of claims 19 to 21, in which the gel is prepared by mixing the constituents under vacuum or under an inert gas atmosphere.

Merckle GmbH

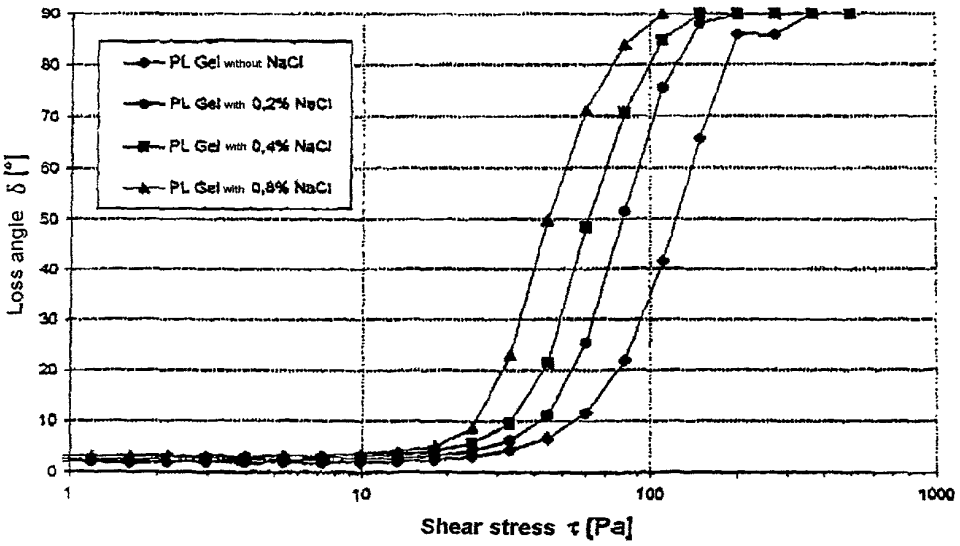
Abstract

Phospholipid gel

A phospholipid gel is disclosed which is stabilized against liquefaction by addition of a tetra-, penta- or hexahydric alcohol or sugar. The gel is suitable for the production of cosmetic and pharmaceutical formulations.

Merckle GmbH

Figure 1A



Firgure 1B

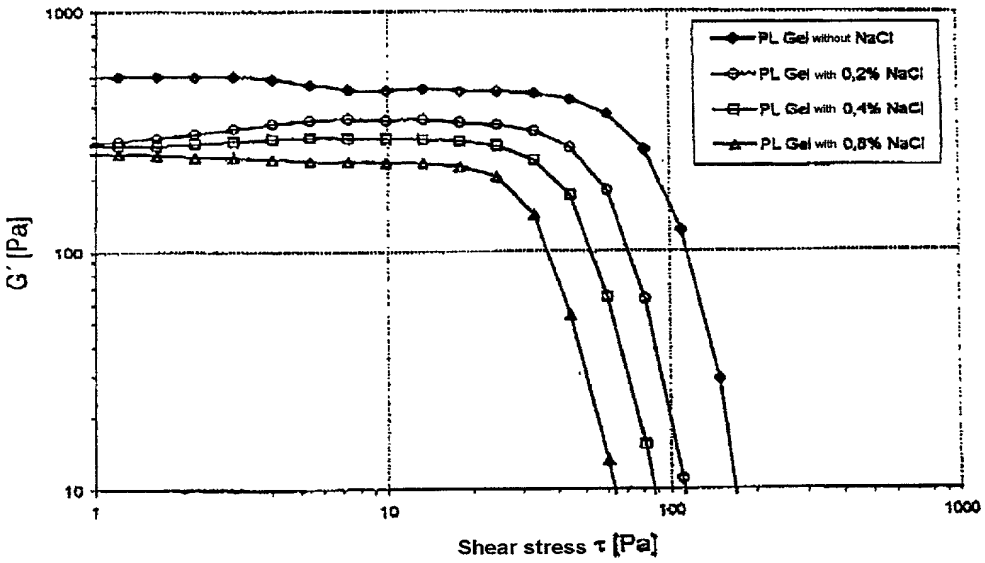

1000
100
10
G´ [Pa]
1
10
100
1000
Shear stress τ [Pa]
PL Gel without NaCl
PL Gel with 0,2% NaCl
PL Gel with 0,4% NaCl
PL Gel with 0,8% NaCl

Figure 2A

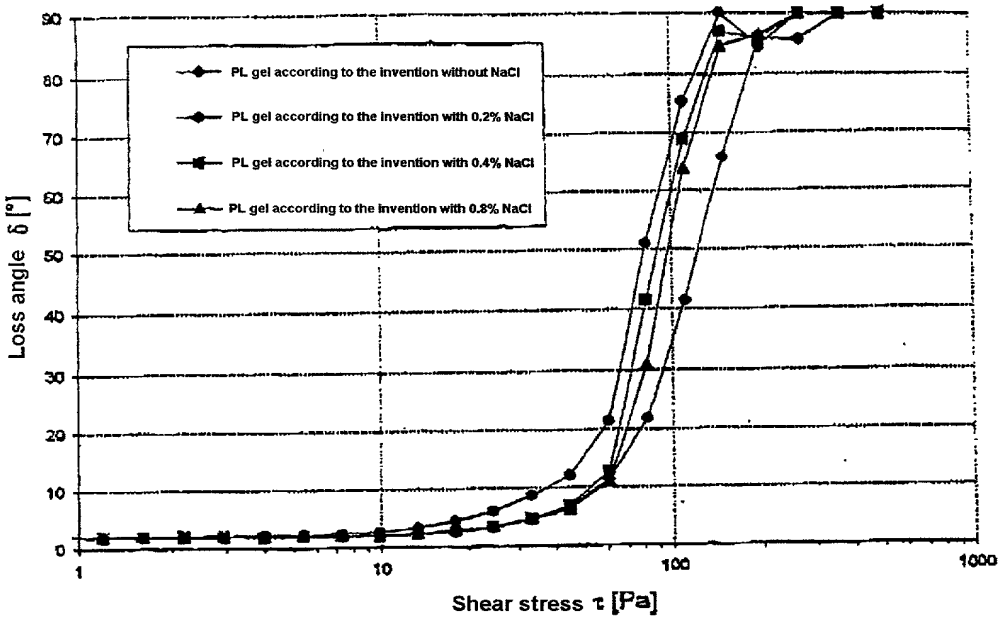

PL gel according to the invention without NaCl
PL gel according to the invention with 0.2% NaCl
PL gel according to the invention with 0.4% NaCl
PL gel according to the invention with 0.8% NaCl
Loss angle δ [°]
Shear stress τ [Pa]
0
10
20
30
40
50
60
70
80
90
1
10
100
1000

Figure 2B

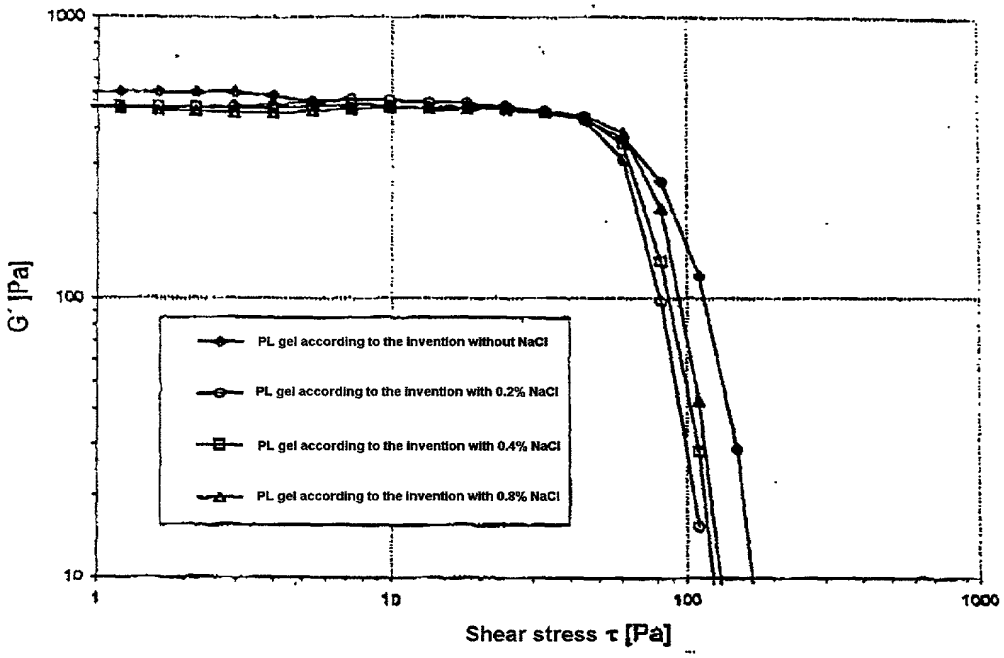

1000
100
10
1
10
100
1000
G´ [Pa]
Shear stress τ [Pa]
PL gel according to the invention without NaCl
PL gel according to the invention with 0.2% NaCl
PL gel according to the invention with 0.4% NaCl
PL gel according to the invention with 0.8% NaCl

Figure 3

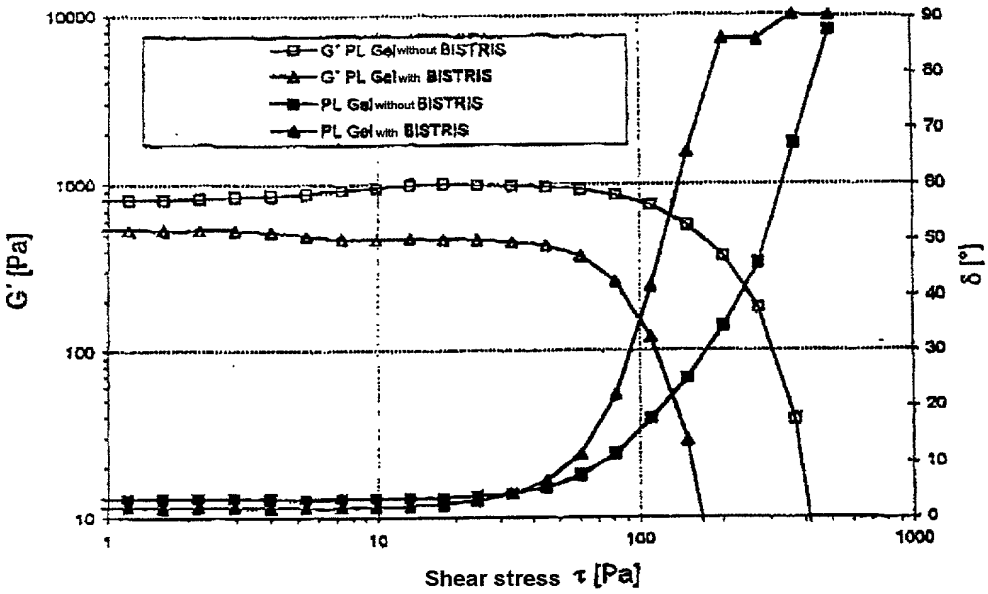
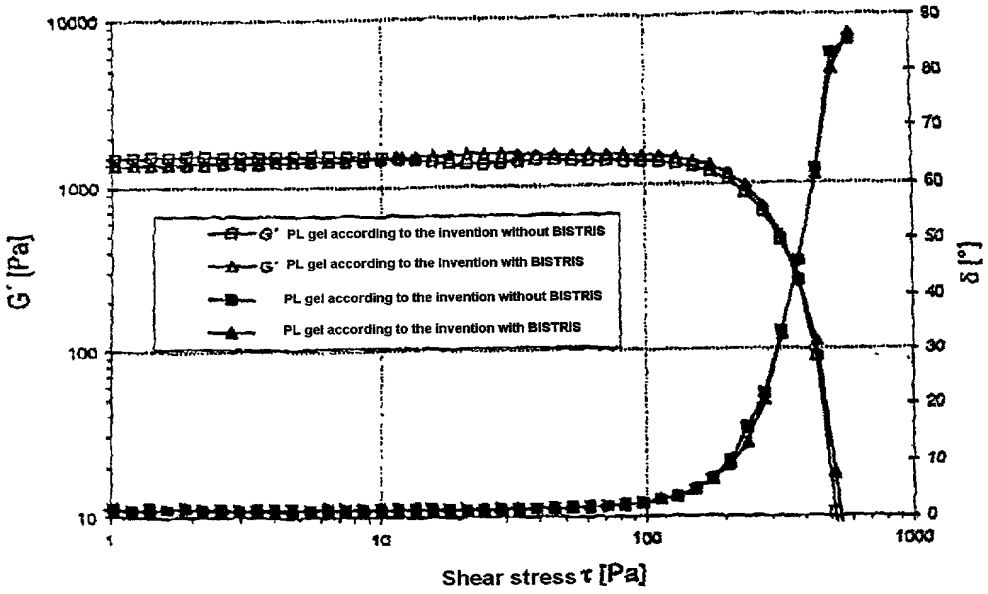

G' PL Gel without BISTRIS
G' PL Gel with BISTRIS
PL Gel without BISTRIS
PL Gel with BISTRIS
G' [Pa]
δ [°]
Shear stress τ [Pa]
10000
1000
100
10
1
10
100
1000
90
80
70
60
50
40
30
20
10
0

Figure 4


10000
1000
100
10
G' [Pa]
90
80
70
60
50
40
30
20
10
0
δ [°]
1
10
100
1000
Shear stress τ [Pa]
G' PL gel according to the invention without BISTRIS
G' PL gel according to the invention with BISTRIS
PL gel according to the invention without BISTRIS
PL gel according to the invention with BISTRIS

COMBINED DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below, next to my name.
I believe I am the original, first, and sole inventor (if only one name is listed below) or an original, first, and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled Phospholipid Gel the specification of which:

____ is attached hereto.
__X__ was filed on February 25, 2002
as United States Application Number 10/069,357
or PCT International Application Number _____
and was amended on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claim(s), as amended by any amendment referred to above. I do not know and do not believe that the claimed invention was ever known or used in the United States of America before my invention thereof, or patented or described in any printed publication in any country before my invention thereof or more than one year prior to this application, that the same was not in public use or on sale in the United States of America more than one year prior to this application, and that the invention has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on an application filed by me or my legal representatives or assigns more than twelve months (for a utility patent application) or six months (for a design patent application) prior to this application.

I acknowledge the duty to disclose all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d), of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed	
19940227.2 (Number)	DE - Germany (Country)	25-August-1999 (Day/Month/Year Filed)	X Yes	____ No
PCT/EP00/07993 (Number)	WO - PCT (Country)	16-August-2000 (Day/Month/Year Filed)	X Yes	____ No
_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	____ Yes	____ No

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below

_____ (Application Number)	_____ Filing Date
_____	_____

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Number)	Filing Date	(Status – patented, pending, abandoned)
(Application Number)	Filing Date	(Status – patented, pending, abandoned)
(Application Number)	Filing Date	(Status – patented, pending, abandoned)

I hereby appoint Toni-Junell Herbert, Registration No. 34,348, Mark R. Shanks, Registration No. 33,781, Joseph G. Contrera, Registration No. 44,628, Shelly Guest Cermak, Registration No. 39,571, Christina M. Gadiano, Registration No. 37,628, Chris Aniedobe, Registration No. 48,293, and Kristin Vidovich, Registration No. 41,448, of SHANKS & HERBERT, telephone (703) 683-3600, with a mailing address at:

TransPotomac Plaza
1033 N. Fairfax St., Suite 306
Alexandria, VA 22314

with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected herewith.

The undersigned hereby authorizes the U.S. Attorneys named herein to accept and follow instructions from undersigned's assignee, if any, and/or, if the undersigned is not a resident of the United States, the undersigned's domestic attorney, patent attorney or patent agent, as to any action to be taken in the Patent and Trademark Office regarding this application without direct communication between the U.S. attorneys and the undersigned. In the event of a change in the person(s) from whom instructions may be taken, the U.S. attorneys named herein will be so notified by the undersigned.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application of any patent issued thereon.

Full Name of Sole/First Inventor: Bernd IBSCHER

Inventor's Signature: _____ Date: 12.4.02

Residence: Blaubeuren, DEX (City, State) Citizenship: Germany (Country)

Post Office Address: Uhlandstrasse 2, 89143 Blaubeuren, GERMANY

2-00 Full Name of Second/Joint Inventor: Ruland FRIDRICH

Inventor's Signature: _____ Date: 12.4.02

Residence: Blaubeuren DEX Citizenship: Germany
(City, State) (Country)

Post Office Address: Steingrubenstrasse 52/2, 89143 Blaubeuren, GERMANY